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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/749,728	12/28/2000	Akihiro Umezawa	766.43	6784

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FITZPATRICK CELLA HARPER & SCINTO
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/749,728	UMEZAWA ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,9-19,21-28,38,39,41,43,44,47-63 and 78-91* is/are pending in the application.

4a) Of the above claim(s) *47-63,78-91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *Claims 1, 6, 9-19, 21-28, 38, 39, 41, 43, 44,* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 2, 2007 has been entered.

The amendment and response filed 12/7/2006 have been entered. Claims 1, 6, 21, 22, 25, 28, 38 have been amended. Claims 2-5, 7, 8, 20, 29-37, 40, 42, 45, 46 have been canceled.

Claims 1, 6, 9-19, 21-28, 38, 39, 41, 43, 44, 47-63, 78-91 are pending, claims 47-63 and 78-91 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. It is noted the withdrawn claims have not been properly identified. Appropriate correction is required in the response to this Office action.

Claims 1, 6, 9-19, 21-28, 38, 39, 41, 43, 44 are under current examination. It is noted the elected invention under current examination is drawn to an isolated pluripotent stem cell capable of differentiating into cardiomyocytes.

Specification

The abstract of the disclosure is objected to because it exceeds 150 words. Correction is required. See MPEP § 608.01(b).

The specification is objected to because the phrase "filed November 1, 2000" should not be deleted (see December 2006 amendment).

Claim Objections

Claim 25 is objected to because of an undefined acronym "BMSC".

Claim 26-28, 38, 39, 41, 43, 44 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. These claims describe a process of inducing stem cell differentiation, and do not further limit the claimed adult stem cells. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 6, 9-19, 21-24, 26-28, 38, 39, 41, 43, 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because the newly submitted amendment inserting "differentiates" in place of "capable of differentiating". For example, in claim 1, "said stem cell differentiates into more than one cell", which encompasses a differentiated cell derived from the differentiation of said stem cell, it is unclear whether the applicant intends to claim an adult stem cell or a differentiated cell, and thus the metes and bounds of the claims are uncertain. Applicant is reminded that the claimed and elected invention is directed to an isolated adult stem cell. For the sake of a compact prosecution, the recitation "differentiates" has been interpreted as reciting "capable of differentiating".

Claim 1 is vague and indefinite because of claim recitation, "said adult stem cell differentiates into more than one cell". Here, the phrase "one cell" embraces both the number of cells, or the phenotype of cells. It appears that applicant intends to claim more than one phenotype of cells, and thus claim should make such clear.

Claim 25 is rejected because it is unclear what the arbitrary custom name "FERM BP-7043" stands for and how, if any, does it limit the mouse BMSC. If it stands for a deposited cell line, such should be clearly set forth. Applicants are reminded that Claims must, under modern claim practice, stand alone to define invention, since limitations are not to be read into claims from specification. In re Van Guens, 988 F.2d 1181; 26 USPQ2d 1057 (Fed. Cir. 1993).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 9-19, 21-28, 38, 39, 41, 43, 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a mixed population of mouse bone marrow stromal cells (BMSCs) for differentiating cardiomyocytes, does not reasonably provide enablement for differentiating cardiomyocytes from a single or purified population of adult bone marrow stem cell(s) identified as CD117+, CD140+, and further bearing various combinations of the surface markers as recited in claims 9-18. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the nature of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Instant claims are directed to an isolated adult bone marrow stem cell that is CD117+, CD140+, and capable of differentiating into more than one cell type, including

a cardiomyocyte. In further preferred embodiments, the stem cells possess various profiles of surface markers, directed to different combinations of surface markers such as CD34+/-, CD144+/-, and a long list of other cell surface markers as recited in claim 15. Given the broadest reasonable interpretation, the claims encompass subsets of stem cells bearing different surface markers but having the same or indistinguishable function. For example, the combination may be CD117+, CD140+, CD34+, CD144+; or CD117+, CD140+, CD34-, CD144+; or CD117+, CD140+, CD34+, CD144-; or CD117+, CD140+, CD34-, CD144-. These cells may further possess or not possess other markers as recited in claims 15-18. Yet, they are all capable of differentiating into cardiomyocytes and other cells as recited in claim 6. The support for the claimed subject matter could be seen in table I of the specification, where these markers were evaluated in mouse bone marrow cells.

However, it is noted that although the applicant started the culture with cloned single cell (Specification, page 86), the markers listed in table I are not identified in a single bone marrow stem cell, rather it was evaluated separately in a population of mouse bone marrow cells (Specification, example 10), where the markers may be positive in one cell but not another, and there is no evidence of any confirmation that a single cell possess a specific surface marker combination as indicated in the claims, and cardiomyocytes are indeed derived from said single cell; there is no evidence of any confirmation that different subsets of stem cells are all capable of differentiating into cardiomyocytes, and at least one other cell type selected from the group consisting of

adiposities, skeletal muscle cells, osteoblasts, vascular endothelial cells, nervous system cells, and hepatic cells, as claimed.

In view of the state of the art pertaining to the bone marrow cell biology, it was well known in the art (*Prockop*, Science 1997;276;71-74) that BMCs have many of the characteristics of stem cell for nonhematopoietic tissues, such as the ability to differentiate into osteoblasts, chondroblasts, adipocytes, and myoblasts (see entire article). It was known in the art that BMCs are capable of secreting cytokines such as the ligand for C-kit (CD117), it was also known in the art that 5-azacytidine could induce BMCs differentiating into rhythmically beating myocytes. It was additionally known in the art that bone marrow cells are heterogeneous, and difficult to clone (e.g. column 2, page 72). The state of the art was such there wasn't an art recognized protocol commonly used to cultivate BMCs, and conditions for differentiating the cells were somewhat species-dependent and were influenced by incompletely defined variable, such as the lot of fetal calf serum. Although the skilled artisans have attempted to prepare more homogeneous populations, it has not been shown whether different laboratories isolate the same cells, nor demonstrated that cultured bone marrow cells retain all the multipotential properties of marrow stromal cells. *Prockop* acknowledges the gaps in understanding the precise molecular events involved in differentiation of a mixed population of bone marrow cells, and pathways of differentiation. Thus, when applicant claims that the CD117+ and CD140+ BMCs, and many other subsets of BMCs are responsible for cardiomyocyte differentiation, sufficient support should be provided.

Such evidence is necessary and art recognized. For example, *Serafini* and *Verfaillie* (Semi Reprod Med 2006;24:379-88) review the state of the art pertaining to adult stem cell biology at the time of a post-filing date, and set forth the art-recognized criteria for identifying an adult stem cell, "INDEED, SOME STUDIES HAVE SUGGESTED THAT CERTAIN CLASSES OF ADULT STEM CELLS CAN UNEXPECTEDLY DIFFERENTIATE INTO CELL TYPES OF ALL THREE GERM LAYERS, SOMEWHAT SIMILAR TO THE DIFFERENTIATION ABILITY OF ESCS" (1st paragraph, page 380), "HOWEVER, PROOF THAT ADULT STEM CELLS HAVE GREATER DIFFERENTIATION ABILITY HAS NOT BEEN PROVIDED BY MOST STUDIES. TO PROVE PLASTICITY, THE FOLLOWING CRITERIA SHOULD BE FULFILLED: **A SINGLE STEM CELL** THAT CAN SELF-RENEW, CAN GIVE RISE TO THE FUNCTIONAL CELL TYPES FROM THE TISSUE WHERE THE STEM CELL ORIGINATED, CAN ALSO GIVE RISE TO CELL TYPES OF AN UNRELATED TISSUE, AND CAN REPOPULATE BOTH TISSUES **ROBUSTLY** *IN VIVO*" (column 2, page 380, emphasis added). According to such standard, instant disclosure fails to establish that the various differentiated cells including cardiomyocytes were indeed derived from a single starting cell that is both CD117+ and CD140+, and further possesses other marker profiles as recited in dependent claims; the specification fails to establish that the cardiomyocytes derived from the single stem cell can repopulate a damaged heart, and/or other unrelated tissue robustly *in vivo*; the specification fails to teach all subsets of stem cells as recited in the claims are capable of differentiating into cardiomyocytes; and thus the specification fails to provide an enabling disclosure for what is now claimed. Accordingly, based on the standard in the pertinent art, the invention does not appear to be enabled.

Given the fact that isolating adult stem cells often requires extensive cultivation *in vitro*, as did the instant specification, wherein the bone marrow cells were cultured for

four months before induced into cardiomyocytes (Specification, page 86), *Serafini* and *Verfaillie* (Seminars Reprod Med 2006;24:379-88) state, "GIVEN THAT THESE CELLS ARE SELECTED FOLLOWING EXTENSIVE MANIPULATION, IT IS POSSIBLE THAT THEY DO NOT EXIST IN VIVO, BUT ARE A CULTURE-INDUCED PHENOMENON" (column 2, page 380). In fact, the CD117+ and CD140+ cells are immortalized cells generated during the culture (Specification, p87), thus, the phenotype appears to have altered compared to the primary bone marrow cells, and thus are derivations of mouse bone marrow cells, may not be directly obtainable from bone marrow in the absence of extensive cultivation and screening. It would have required undue experimentation for the skilled in the art to obtain these cells since the spontaneous immortalization is an unpredictable event.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following art rejection applied because, in the absence of evidence to the contrary, the claimed cells appear to embrace the prior art cells. In view of the Office policy for compact prosecution, all issues relevant will put forward.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 9-11, 15, 16, 19, 21-23, 26-28, 38, 39, 41, 43, 44 are newly rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Wakitani et al* (Muscle & Nerve 1995;18:1417-26).

Wakitani et al disclose isolated adult rat bone marrow cells capable of differentiatng into more than one mesenchymal cell phenotypes including bone, cartilage, and adipocytes. Upon administration of 5-azacytidine, long, multinucleated myotubes were observed in the culture. *Wakitani et al* concluded culture-propagated rat bone marrow mesenchymal stem cells appear to have the capacity to be induced to differentiate in vitro into myogenic and adipocytic phenotypes, and may provide a source for myoprogenitor cells which could function in clinically relevant myogenic regeneration.

Although *Wakitani et al* do not teach surface marker profile of the cells, since the cells were obtained from bone marrow, and having the functional capability as the claimed cells, the cells disclosed by *Wakitani et al* appear to contain the same type or obvious variants of instantly claimed cells. Thus, the claimed invention as a whole was

at least *prima facie* obvious, if not anticipated, by the reference, in the absence of sufficient, clear and convincing evidence to the contrary.

MPEP 2112 states, "[O]NCE A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFT TO THE APPLICANT TO SHOW AN OBVIOUS DIFFERENCE". "[T]HE PTO CAN REQUIRE AN APPLICANT TO PROVE THAT THE PRIOR ART PRODUCTS DO NOT NECESSARILY OR INHERENTLY POSSESS THE CHARACTERISTICS OF HIS [OR HER] CLAIMED PRODUCT. WHETHER THE REJECTION IS BASED ON INHERENCY' UNDER 35 U.S.C. 102, ON PRIMA FACIE OBVIOUSNESS' UNDER 35 U.S.C. 103, JOINTLY OR ALTERNATIVELY, THE BURDEN OF PROOF IS THE SAME...[FOOTNOTE OMITTED]." THE BURDEN OF PROOF IS SIMILAR TO THAT REQUIRED WITH RESPECT TO PRODUCT-BY-PROCESS CLAIMS. (QUOTING *IN RE BEST,* 562 F.2D 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). SEE ALSO *IN RE FITZGERALD,* 619 F.2D 67, 70, 205 USPQ 594, 596 (CCPA 1980) EX PARTE PHILLIPS, 28 USPQ 1302, 1303 (BPBI 1993), AND EX PARTE GRAY 10 USPQ2D 1922, 1923 (BPAI 1989). Such prove requires factual evidence demonstrating that actual, unobvious differences exist (or that the claimed products are functionally different than those taught by the prior art) and to establish patentable differences.

Claims 1, 6, 9-11, 15, 16, 21-24, 26-28, 38, 39, 41, 43, 44 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Shi et al* (Blood 92:362-367, 1998), and as evidenced by *Prockop et al* (Science 1997;276;71-74).

Shi et al teach a subset of human bone marrow cells that is CD34+, and derivation of endothelial cells from the bone marrow cells (see the entire article). Although *Shi et al* do not particularly teach that the bone marrow cells are capable of differentiated into other cell types, this was known in the art as evidenced by *Prockop et al*. Although *Shi et al* do not teach whether the recited markers are present in the subset, since the cells were obtained from bone marrow, capable of differentiating into at least vascular endothelial cells, and thus appear to contain the same type or obvious variation of instantly claimed cells.

In the remarks, the applicant asserted that the surface markers are not inherent property of the prior art cells. In response, such assertion needs to be supported by factual evidence demonstrating that actual, unobvious differences exist (or that the claimed products are functionally different than those taught by the prior art) and to establish patentable differences.

In the remarks, the applicant indicated that the claims have been amended as an examiner of record suggested in the 11/16/05 Office action.

A review of the previous Office action would find this is not the case. The cited sentence indicated that the instantly reference anticipates instant claims because the claims fail to set forth distinguishable characteristics that would set the instantly claimed cells apart from the prior art of record.

Accordingly, *Shi et al* anticipates or renders obvious of instantly claimed invention.

Claims 1, 6, 9-11, 15, 16, 19, 21-23, 26-28, 38, 39, 41, 43, 44 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Makino et al* (Journal of Clinical Investigation. 103:697-705, 1999).

Makino et al teach mouse bone marrow cells that are Nkx2.5/Csx+ and GATA4+, which are capable of differentiating into many cells of mesenchymal lineage (e.g. column 2, page 697), and would differentiate into cardiomyocytes upon exposure to 5-azacytidine (e.g. fig. 1). Although *Markino et al* do not teach whether the recited markers are present in these bone marrow cells, since they were obtained from mammalian bone marrow, capable of differentiating into various cells of mesenchymal lineage, and thus appear to be the same type or obvious variation of the cells as instantly claimed.

Accordingly, *Markino et al* anticipates or renders obvious of instantly claimed invention.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
October 12, 2007